REMARKS

Upon entry of the amendments submitted herewith, claims 61, 65-70, 72-76, and 84-99 will be pending in the instant application. Claims 1-60 remain canceled without prejudice. Claims 62-64, 71, and 77-83 are canceled herein without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the canceled claims in one or more continuing applications. Claims 61, 65, 66, 70, 72, and 73 are currently amended. Claims 84-99 are newly introduced. As detailed below, support for the amendments and newly introduced claims is found throughout the specification and claims as originally filed, thus no new matter is introduced.

For example, support for the amendments to claims 61 and 70 is found at least at page 14, lines 6-10 and page 9, lines 14-17 of the specification. Claims 65 and 72 are amended to clarify that the recited antisense compound is a single-stranded antisense oligonucleotide, support for which is found at least at page 11, lines 29-30 and the claims as originally filed. Claims 66 and 73 are amended for clarity. Support for new claims 84, 85, 92, and 93 is found at least at page 43 line 29 to page 44 line 6 of the specification. Support for new claims 86-89 and 94-97 is found at least at page 41, lines 15-21 and page 58, lines 19-21 of the specification. Support for new claims 90, 91, 98 and 99 is found at least at page 28, line 30 to page 29, line 21 of the specification, and in the claims as originally filed in International Application PCT/US04/10946.

Applicants provide herewith an Information Disclosure Statement, and respectfully request that the Examiner consider and initial the references cited therein.

Priority

The Examiner alleges that parent applications PCT/US04/10946 and USSN 10/418,780 do not support the instant claims, either implicitly or explicitly, and that consequently the instant application is entitled priority to July 10, 2006, which is the filing date of the instant application. Specifically, the Examiner alleges that parent applications PCT/US04/10946 (the International Application) and USSN 10/418,780 have support for methods of reducing hyperlipidemia, and lowering serum triglyceride and cholesterol levels in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid

molecule encoding apolipoprotein C-III, but that these methods do not support the instantly claimed methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, or reducing adipose tissue. Further, the Examiner alleges that support for the instantly claimed methods is found only in the instant application, but not in any of the applications to which the instant application claims priority. Applicants respectfully disagree and submit that the instant claims are entitled to at least the priority date of International Application PCT/US04/10946, filed April 15, 2004 and published November 4, 2004. As claims 77-83 are canceled herein, the following remarks are directed to the methods recited in claims 61 and 70, and the claims depending therefrom.

Support for methods of ameliorating hepatic steatosis and lowering liver triglyceride levels is found throughout the specification of International Application PCT/US04/10946, to which the instant application claims priority. For example, page 29 of the International Application states that "apolipoprotein C-III inhibitors are useful in the treatment of hypertriglyceridemia, abnormal lipid metabolism, abnormal cholesterol metabolism, atherosclerosis, hyperlipidemia, diabetes, including Type 2 diabetes, obesity, cardiovascular disease, coronary artery disease, among other disorders relating to abnormal cholesterol metabolism or otherwise." The definition of hepatic steatosis, and its link to at least the aforementioned conditions, is found at page 102 of the International Application, which states "hepatic steatosis refers to the accumulation of lipids in the liver, or 'fatty liver,' which is frequently caused by alcohol consumption, diabetes and hyperlipidemia and can progress to end-stage liver damage." Additionally, working examples are provided to demonstrate Applicants' finding that antisense compounds targeted to apolipoprotein C-III reduced liver triglyceride content (see pages 102-103 of the International Application). Furthermore, page 103 of the International Application states that, owing to their ability to reduce liver triglyceride content, "antisense compounds targeted to apolipoprotein C-III are candidate therapeutic agents for the prevention or amelioration of hepatic steatosis."

For at least the aforementioned reasons, the instant claims to methods of ameliorating hepatic steatosis and lowering liver tissue triglyceride levels are amply supported by the International Application PCT/US04/10946. Further, the instant application is the U.S. National Stage of the International Application PCT/US04/10946.

As such, Applicants submit that the instant application is entitled to the priority date of the International Application, which was filed on April 15, 2004.

Double Patenting

Claims 61-83 are provisionally rejected on the grounds of non-statutory double patenting, as allegedly not patentably distinct from claims 23, 38, 39, 45-62, and 64 of copending US Application Publication No. 20040208856. Applicants respectfully request that the provisional double-patenting rejection of the currently pending claims be held in abeyance until such time as the instant claims are found to be allowable. Claims 62-64, 71, and 77-83 are canceled herein, rendering the rejection of these claims moot.

Rejection under 35 U.S.C. § 112, Enablement

Claims 61-83 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising any route of administration of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO: 4). The Examiner further alleges that the specification does not enable any person skilled in the art to which it pertains, or with which is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner notes that the rejection is a scope enablement rejection. Office Action at page 6. Applicants respectfully disagree and submit that pending claims are adequately enabled by the specification. Without acquiescing to the rejection, claims 62-64, 71, and 77-83 are canceled herein, thus the following remarks address the rejection as it relates to the claims that are pending following entry of the present amendment.

An application enables the claims "if one skilled in the art, after reading the [] disclosure [], could practice the invention claimed ... without undue experimentation." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). "But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus., Inc., v. Guardian Indus.*

Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)). Whether the amount of experimentation required to practice the full scope of the invention is undue can be determined using the well-known Wands factors, which include the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention bases on the content of the disclosure. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

In order to make an enablement rejection, the PTO has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See M.P.E.P.* § 2164.04. A specification teaching how to make and use the claimed subject matter must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *Id.* Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on the applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See M.P.E.P. § 2164.05.* "The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." *Id.* (underline in original)

The Specification Provides Ample Guidance to Practice the Claimed Methods

The Examiner states that there is no guidance in the specification to suggest that "methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising the intraperitoneal injection of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO: 11) would be effective to result in methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO: 4)." Office

Action at page 8. The Examiner relies on Agrawal et al. to support the assertion that "it is unpredictable to determine the antisense ability of an oligonucleotide to inhibit target gene expression based purely on complementarity to a target RNA." The Examiner quotes from Agrawal et al. "The initial step in selecting an antisense oligonucleotide is to choose an appropriate target sequence on the mRNA molecule. Antisense technology has been hampered to some extent by limited knowledge as to the base-pairing accessibility of mRNA target sites *in vivo*. Although a number of models that predict RNA folding are available, their usefulness for predicting the most plausible *in vivo* RNA structure is limited" (see Agrawal, pages 76-77). This passage from Agrawal et al. has been removed from its context: the unpredictability of RNA folding in vivo and the impact of that unpredictability in selecting a target sequence. In this passage, Agrawal et al. discuss the use of RNA folding and RNA structure to identify accessible target sites within a target RNA. The predictability of RNA folding *in vivo* is irrelevant in determining enablement of the instant claims, which recite methods of ameliorating hepatic steatosis and lowering liver tissue triglyceride levels. Applicants have not merely described predicted RNA folding "to choose an appropriate target sequence on the mRNA molecule" as criticized by Agrawal et al. (pages 76-77). Moreover, Agrawal et al. subsequently states that "*in vitro* methods can be used to test the accessibility of mRNA sites by oligonucleotides, but this has met with limited success. It is considered preferable, therefore, to screen a number of oligonucleotides that encompass different regions on RNA to identify a set of optimal target sites, including the 5'-and 3'-untransated regions (UTRs), initiation codon site, coding region and intron-exon junctions." (Agrawal et al. at page 77). As evidenced by the numerous examples of antisense compounds disclosed and tested in the instant specification, Applicants have, in fact, performed such screening of a number of compounds that target different regions on nucleic acid molecules encoding apolipoprotein C-III. The instant specification explicitly describes not only antisense sequence complementary to SEQ ID NO: 11 (mouse apolipoprotein C-III, 21 antisense sequences) but also exemplifies antisense sequences complementary to SEQ ID NOs 4 and 18 (human apolipoprotein C-III; 91 antisense sequences). The specification additionally provides antisense sequences complementary to SEQ ID NOs 225 and 226 (rat apolipoprotein C-III; 119 antisense sequences) and to SEQ ID NO: 352 (hamster

apolipoprotein C-III; 48 antisense sequences). Additionally, many of the disclosed antisense compounds are tested for their ability to inhibit the expression of apolipoprotein C-III; see, for example, Tables 1, 4, and 5, illustrating *in vitro* testing data of antisense sequences complementary to SEQ ID NOs 4 and 18 (human); Table 2 and 6, illustrating *in vitro* testing data of antisense sequences complementary to SEQ ID NO: 11 (mouse); and Tables 11, 13, and 14 showing *in vitro* testing data of antisense complementary to SEQ ID NOs 225 and 226 (rat).

The data obtained from the *in vitro* studies was used to guide the selection of candidate antisense compounds to be used in *in vivo* models of hyperlipidemia. While many working examples are provided in the specification, of particular relevance to the instant claims are Examples 25, 26, 27 and 28, which describe the testing of antisense compounds targeted to apolipoprotein C-III in a mouse model of hyperlipidemia. The candidate antisense compounds were tested for, among other things, their effects on hepatic steatosis and liver tissue triglyceride levels. A review of the results demonstrates that treatment with the candidate antisense compounds reduced hepatic steatosis and liver tissue triglyceride levels (see Example 28, page 103), and that these effects occurred concomitantly with reductions in liver apolipoprotein C-III mRNA levels. Thus, Applicants have demonstrated that *in vitro* testing data can be used to guide the selection of antisense compounds for further *in vivo* testing to determine their efficacy as therapeutic agents for the amelioration of hepatic steatosis and the lowering of liver tissue triglyceride levels. Thus, the instant application provides the very sort of guidance that Agrawal describes as "preferable."

In view of the foregoing disclosure, Applicants respectfully submit that the specification provides ample guidance for the selection of antisense compounds targeted to nucleic acid molecules encoding apolipoprotein C-III, including SEQ ID NO: 4, for use in the claimed methods. Furthermore, Applicants have described routine methods for making antisense compounds targeted to a nucleic acid molecule encoding apolipoprotein C-III and routine methods for determining whether these antisense compounds are capable of inhibiting the expression of apolipoprotein C-III *in vitro*. As such, using the examples set forth in the specification, the skilled artisan could test the ability of antisense compounds complementary to SEQ ID NO: 4 *in vitro*, and subsequently test the

antisense compounds *in vivo* to identify those capable of ameliorating hepatic steatosis and lowering liver tissue triglyceride levels.

The Specification Enables Systemic Delivery of Antisense Compounds

The Examiner alleges that the claims are "so broad as to include systemic delivery of antisense compounds that specifically hybridize with a nucleic acid molecule encoding apolipoprotein C-III, where the prior art teaches that systemic delivery of oligonucleotides is highly unpredictable." Office Action at page 9. The Examiner asserts that "the scope of the claims requires knowledge of how to routinely systemically deliver antisense oligonucleotides *in vivo* to result in a therapeutic effect." Office Action at pages 9-10.

Applicants submit that the instant specification fully enables the systemic delivery of antisense compounds targeted to nucleic acid molecules encoding apolipoprotein C-III. For example, pages 43-44 of the instant specification enumerate routes of administration for the systemic delivery of antisense oligonucleotides, including parenteral delivery (see, for example, the specification at pages 43-44). Additionally, the working examples illustrate that antisense oligonucleotides administered via systemic administration (e.g. intraperitoneal) are able to reach the target tissue and effect the reduction of the target mRNA, as well as result in the therapeutic effects of ameliorating hepatic steatosis and lowering liver tissue triglyceride levels. Furthermore, these *in vivo* effects are demonstrated for not one, but for at least four different antisense compounds.

The Examiner asserts that in order to practice the claimed methods, "one would first have to establish that the feasibility of antisense therapy for one antisense demonstrates the feasibility of antisense therapy for a wholly different antisense oligonucleotide." Office Action at pages 9-10. The Examiner further asserts that devising successful methods as claimed would require "extensive trial and error experimentation, with a large number of patients and patient controls..." Office Action at page 10. Applicants respectfully remind the Examiner that undue experimentation is not measured by the amount of time, expense, or quantity of routine experimentation that is involved in implementing the disclosed methods (see In re Wands 858 F.2d 731 (Fed. Cir. 1988). It is well-established that "[t]he fact that some experimentation is necessary does not

preclude enablement" *PPG Indus., Inc., v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The instant specification describes in detail routine procedures for identifying antisense compounds capable of inhibiting the expression of apolipoprotein C-III and administering the antisense compounds to ameliorate hepatic steatosis and lower liver tissue triglyceride levels. Furthermore, the instant specification demonstrates with working examples that antisense compounds targeted to apolipoprotein C-III are effective at reducing hepatic steatosis and lowering liver tissue triglyceride levels. Thus, the feasibility of antisense inhibition of apolipoprotein C-III via systemic administration for the achievement of therapeutically desirable outcomes has been demonstrated in the instant specification.

Applicants have provided through illustrative examples both *in vitro* and *in vivo* methodologies for the implementation of the claimed methods, and thus one skilled in the art would be able to make and use the claimed invention using the application as a guide, without the need for undue experimentation. Accordingly, Applicants respectfully request that the enablement rejection be withdrawn.

In view of the foregoing remarks, Applicants submit that newly added claims 84-99 are likewise fully enabled by the specification.

Rejection Under 35 U.S.C. § 102

Claims 61-83 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Crooke et al. (2005). As described herein, Applicants submit that the instant application is entitled to the priority date of International Application PCT/US04/10946, which was filed on April 16, 2004. As such, the Crooke et al. publication of 2005 is not available as a reference under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request withdrawal of this rejection.

Conclusion

Applicants submit that the foregoing represents a full and complete reply to the outstanding Office Action. Should any unresolved issues remain, the Examiner is invited to contact the undersigned for resolution of such issues.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to Deposit Account Number 500252, referencing Attorney Docket No. BIOL0004USA.

Respectfully submitted,

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